The dramatic presentation of this disorder with fever and mixed hepatocellular and cholestatic liver function abnormalities suggests alternative diagnoses, but inquiry regarding quinine use is helpful. This commonly used remedy for a frequent clinical problem, especially among elderly patients, justifies increased awareness of this little-recognized manifestation of quinine use.

REFERENCES

1. Webster LT Jr: Drugs used in the chemotherapy of protozoal infections, chap 41, *In* Gilman AG, Rall TN, Nies AS, Taylor P (Eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th edition. Elmsford, NY, Pergamon Press, 1990, pp 991-994

2. Connolly PS, Shirley EA, Wasson JN, Nierenberg DW: Treatment of nocturnal leg cramps: A crossover trial of quinine vs vitamin E. Arch Intern Med 1992; 152:1877-1880

3. Knobler H, Levij IS, Gavish D, Chajek-Shaul T: Quinidine-induced hepatitis: A common and reversible hypersensitivity reaction. Arch Intern Med 1986; 146:526-528

4. Punukollu RC, Kumar S, Mullen KD: Quinine hepatotoxicity: An underrecognized or rare phenomenon? Arch Intern Med 1990; 150:1112-1113

5. Katz B, Weetch M, Chopra S: Quinine-induced granulomatous hepatitis and vasculitis (Letter). BMJ 1990; 300:613

6. Mathur S, Dooley J, Scheuer PJ: Quinine-induced granulomatous hepatitis and vasculitis (Letter). BMJ 1990; 300:613

7. Rosellini SR, Costa PL, Gaudio M, et al: Hepatic injury related to enalapril (Letter). Gastroenterology 1989; 97:810

8. Bellary SV, Isaacs PET, Scott AWM: Captopril and the liver (Letter). Lancet 1989; 2:514

9. Rahmat J, Gelfand RL, Gelfand MC, Winchester JF, Schreiner GE, Zimmerman HJ: Captopril-associated cholestatic jaundice. Ann Intern Med 1985; 102:56-58

10. Larrey D, Babany G, Bernuau J, et al: Fulminant hepatitis after lisinopril administration. Gastroenterology 1990; 99:1832-1833

Severe Atypical Behçet's Syndrome

DAVID R. PARK, MD
W. CONRAD LILES, MD, PhD
PHILLIP KIRBY, MD
Seattle, Washington

BEHÇET'S SYNDROME is a chronic relapsing inflammatory condition of unknown cause.[1,2] Major clinical features of this syndrome include recurrent aphthous stomatitis, genital ulcers, cutaneous vasculitis, uveitis, synovitis, and meningoencephalitis,[1-6] although any organ may be affected by the multisystemic vasculitis that characterizes this disorder.[5,6] No pathognomonic clinical, serologic, or pathologic features have been identified. The diagnosis continues to be based on the recognition of a number of compatible clinical manifestations of the syndrome. An international study group recently agreed that diagnosis should be based on the presence of recurrent oral ulcers associated with at least two of the following criteria: genital ulcers, uveitis, typical skin lesions, or confirmed pathergy (the formation of a sterile cutaneous pustule at the site of a needle puncture).[6] Diagnosis is often complicated by the asynchronous and delayed appearance of key clinical features of Behçet's syndrome in a given patient.[1,3] Corticosteroid treatment continues to be important,[1-3,5] but recent evidence indicates that cytotoxic therapy with an agent like chlorambucil may be necessary to arrest severe manifestations of Behçet's vasculitis such as uveitis and meningoencephalitis.[5,7]

We report a case with features of Behçet's syndrome causing severe multisystemic disease in a young man. This case is unique because of the rapid clinical evolution of life-threatening disease, the severity of end-organ effects, and the successful use of intravenous pulse-dose cyclophosphamide therapy.

Report of a Case

A previously healthy 34-year-old man presented to the Harborview Medical Center, Seattle, Washington, with polyarthritis and a rash. Two weeks before admission, he had a cough productive of scant white sputum, and redness and pain developed in his left eye. Three days before admission, he had fever, rigors, left hip pain, and swelling of the elbows. On the day before admission, a mildly pruritic rash developed on his face that spread to involve his chest, back, and arms. With the onset of postural lightheadedness and diffuse myalgias, he came to the hospital and was admitted. The past medical history was notable for several episodes of penile shaft ulceration that resolved without medical attention. There was no history of headache, photophobia, visual changes, nausea, vomiting, diarrhea, dysuria, urethral discharge, or insect bites.

On examination the patient was thin and grimaced in pain with movement of his extremities. His temperature was 37.5°C, the pulse rate was 120 beats per minute, respirations were 18 per minute, and the blood pressure was 130/100 mm of mercury. A cutaneous eruption consisting of scattered pustules and papules with hemorrhagic crusts and surrounding erythema involved the face, upper trunk, and arms (Figure 1). The palms, nail beds, and lower body were spared. The left conjunctival membrane was injected; the fundi and uveal structures were normal. There were several small buccal mucosal ulcers. No heart murmur was heard. The liver and spleen were not enlarged. A small ulcer of the dorsal penile shaft was present. The elbows, knees, and right ankle were inflamed and swollen in a fusiform pattern. Passive range of motion produced severe discomfort though no effusions were evident. Initial laboratory data included a normal hematocrit, platelet count, serum chemistry values, and urinalysis. The leukocyte count was 13.0×10^9 per liter (normal 4.3 to 10.0). The blood smear and leukocyte differential count were normal, as were prothrombin and activated partial thromboplastin times. Two blood specimens and a urethral specimen were obtained for culture.

A presumptive diagnosis of disseminated gonococcal infection was made, and empiric antibiotic treatment was initiated. On the second day of the hospital stay, fever and fusiform swelling of the hands, wrists, and forearms de-

(Park DR, Liles WC, Kirby P: Severe atypical Behçet's syndrome. West J Med 1994; 160:60-63)

From the Department of Medicine, Divisions of Pulmonary and Critical Care Medicine (Dr Park), Allergy and Infectious Diseases (Dr Liles), and Dermatology (Dr Kirby), University of Washington School of Medicine, Seattle.

This study was supported by grant AI 07044-16 from the National Institutes of Health (Dr Liles).

Reprint requests to David R. Park, MD, Div of Pulmonary and Critical Care Medicine, Dept of Medicine, ZA-62, Harborview Medical Center, Seattle, WA 98104.

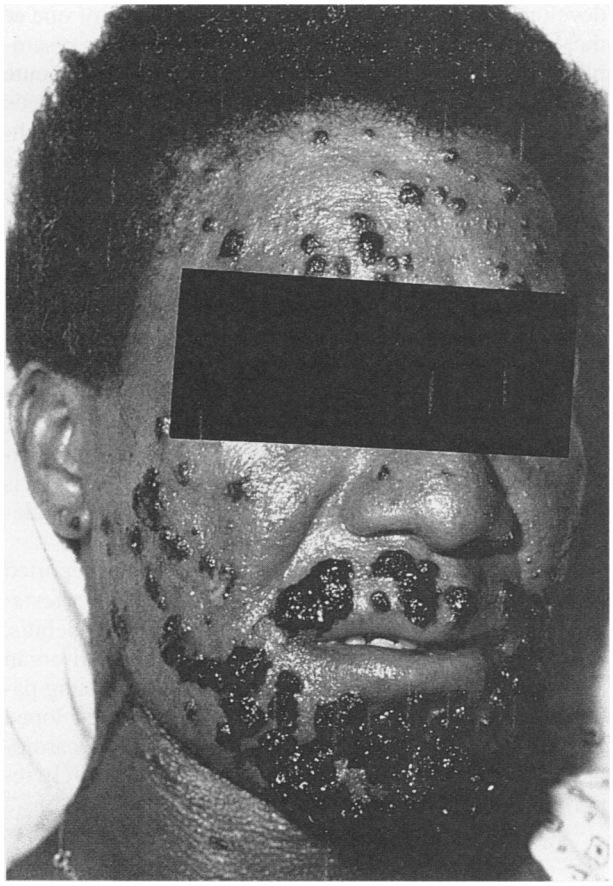

Figure 1.—The patient's face on the third day of hospitalization shows crusting hemorrhagic papules and pustules.

veloped. Specimens were obtained from an unroofed pustule for herpes group immunofluorescent staining and culture. Two days later, he remained febrile with more pronounced periarticular inflammation and the continuing development of new skin papules in the involved areas. All cultures remained negative for bacterial or viral organisms. A punch biopsy specimen of an upper chest papule revealed focal perifollicular dermal and epidermal infiltrates of neutrophils without cytopathic or vasculitic changes (Figure 2). Based on a provisional diagnosis of Sweet's syndrome, all antimicrobial agents were stopped and a regimen of prednisone, 80 mg orally per day, was begun. Within 48 hours, substantial resolution was noted in the rash and periarticular inflammation.

On the fifth day of his hospital stay, however, the patient had nausea, vomiting, and painful abdominal distention due to intestinal ileus demonstrated by abdominal radiographs. Over the ensuing 48 hours, the abdominal symptoms worsened and occult blood was noted in the stool. Tachypnea developed, and a lobar infiltrate was noted on a chest radiograph. Broad-spectrum antibiotic therapy was resumed after additional specimens for culture were obtained. New crusted pustules were noted at several antecubital venipuncture sites. Biopsy of an antecubital pustule revealed histologic features identical to those of the original skin biopsy. Serial abdominal radiographs revealed increasing bowel dilatation with irregular bowel wall thickening, and culture of blood drawn on the seventh day of his hospital stay grew *Serratia marcescens*. On the tenth day of his hospital stay, the patient had diffuse pulmonary infiltrates and acute respiratory failure requiring the use of an endotracheal tube and mechanical ventilation. Endotracheal secretions were bloody. Vasopressor infusions were necessary to maintain adequate blood pressure. A pericardial friction rub was noted, and an electrocardiogram revealed diffuse ST-segment elevation consistent with acute pericarditis. Echocardiography showed normal valves and a large pericardial effusion without evidence of pericardial tamponade. Obtundation prompted a computed tomographic scan of the head and cerebrospinal fluid examination, both yielding normal results. Despite the substitution of intravenous methylprednisolone sodium succinate, 1 gram three times a day, for prednisone and the addition of intravenous immune globulin, 1 gram per day, no notable clinical improvement was evident by the 12th day of hospital stay.

Based on the suspicion of an underlying aggressive systemic vasculitis, cyclophosphamide, 1 gram, was administered as a single intravenous dose. Substantial clinical improvement over the next five days led to successful

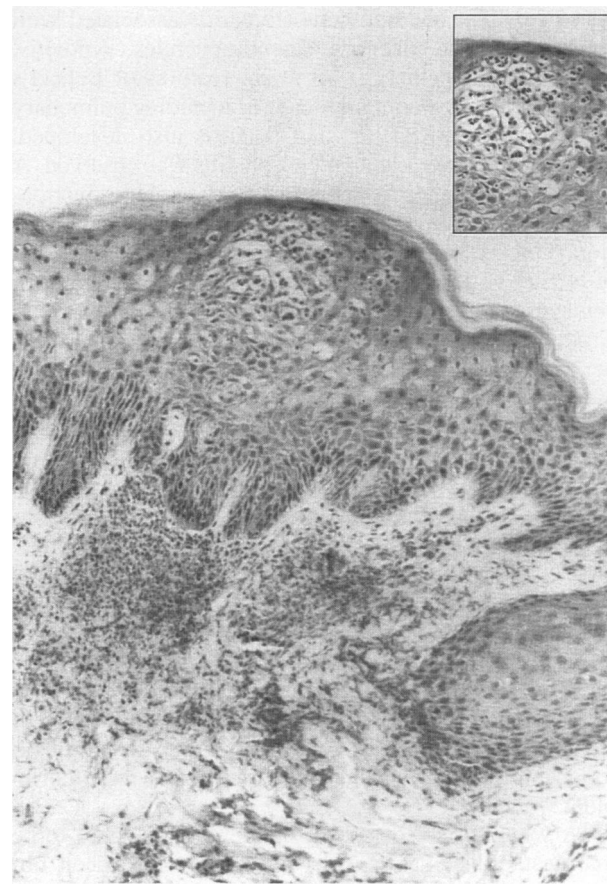

Figure 2.—A punch biopsy of the skin (original magnification × 200) shows dermal and epidermal edema and dense focal acute inflammatory infiltration. No distinct vasculitic changes are present. The inset shows a focal epidermal collection of neutrophils.

removal of the endotracheal tube. His ileus resolved, permitting oral intake, and the patient was moved from the intensive care unit on the 24th day in the hospital. Nine days later, all signs of rash, mucosal ulceration, and arthritis had resolved. Chest radiographs and electrocardiograms had returned to normal. The patient was discharged in satisfactory condition on a maintenance regimen of prednisone, 30 mg orally twice a day, and chlorambucil, 4 mg orally per day. Additional laboratory studies included tests for human immunodeficiency virus antibody, syphilis, antinuclear antibodies, and rheumatoid factor, all of which were negative. Human leukocyte antigen typing revealed the presence of HLA-B45 and B49 antigens but not HLA-B5, B27, or B51.

Over the 12 months since discharge, prednisone and chlorambucil have been tapered to doses of 5 mg daily and 1 mg daily, respectively. Penile ulcers have recurred on several occasions; a painful knee effusion occurred once. No increases in drug doses have been necessary. There has been no recurrence of rash or gastrointestinal or cardiopulmonary symptoms. Adverse effects have been limited to mild asymptomatic aminotransferase elevations and facial acne that responded to oral antibiotic therapy.

Discussion

Our patient had aphthous stomatitis associated with recurring genital ulcers, cutaneous pustules, synovitis, and cutaneous pathergy—all major features of Behçet's syndrome.[1,5,6] Less common features including pulmonary hemorrhage, pericarditis, and enteritis also developed. Neither uveitis nor meningoencephalitis was observed. A diagnosis of Behçet's syndrome best explains our patient's clinical presentation. Although recurrent aphthous stomatitis is a necessary part of the case finding definition of Behçet's syndrome, it is recognized that a small percentage of patients have no oral mucosal involvement.[6] Crohn's disease may present in a remarkably similar manner.[8] The diagnostic distinction often requires intestinal biopsy,[9,10] which our patient did not undergo. The arthritis of Crohn's disease typically occurs after chronic intestinal symptoms.[8] This feature and the presence of cutaneous pathergy favor a diagnosis of Behçet's syndrome. Gram-negative bacteremia undoubtedly complicated our patient's course but occurred after seven days in the hospital and was likely due to gut mucosal involvement by his primary inflammatory disease.

Behçet's syndrome has been observed primarily in Asian and Eurasian populations,[4] but rarely reported in African Americans. Although the clinical course of Behçet's syndrome is variable, in our patient it was unusually accelerated and severe. Interestingly, it is thought to be more severe in young men and most remittent in older women.[2,11]

A wide variety of skin lesions, all considered to be manifestations of cutaneous vasculitis, have been observed in Behçet's syndrome. These include papules, pustules, vesicles, pyoderma, folliculitis, and nodules resembling erythema nodosum.[1,3,4] Our patient presented with a pustular eruption of the face and upper trunk that rapidly developed hemorrhagic characteristics. Biopsy of one of these lesions revealed structural features closely resembling those described in Sweet's syndrome.[12] An acute neutrophilic dermatosis with clinical features of Sweet's syndrome is a rare but recognized presentation of Behçet's syndrome. As in our patient, these skin lesions usually respond rapidly to treatment with parenteral corticosteroids. In addition, our patient showed considerable cutaneous pathergy.[13] This curious phenomenon is common in Turkish patients with Behçet's syndrome; being unique to Behçet's syndrome, it is rare in white patients.[14] Biopsy of a pathergic lesion from our patient revealed structure remarkably similar to that observed in the spontaneous lesion.

A symmetric arthritis affected the ankles, knees, wrists, and elbows of our patient. Recurrent seronegative arthritis, primarily involving the knees, ankles, and wrists, is noted in 50% to 60% of patients.[1-3,15] It is usually nondestructive and steroid responsive, as in our patient.

Involvement of the cardiovascular system is reported in 7% to 29% of patients.[3] The predominant manifestations are arterial aneurysms, superficial thrombophlebitis, and thromboses of large veins and arteries.[1,3] End-organ infarction, including myocardial infarction in young patients, can occur. A large pericardial effusion developed in our patient, and he had pronounced electrocardiographic changes of pericarditis, a complication rarely reported in the literature.[3]

Gastrointestinal involvement, as seen in our patient, is a rare manifestation. The clinical presentation usually mimics Crohn's disease of the colon with discrete ulcers involving any portion of the large bowel and occasionally the distal ileum.[1,3,9,10] Perforations of the large bowel and ileum requiring emergent surgical intervention have been reported.[1,10] Our patient's gastrointestinal complications were limited to hemorrhage and ileus that responded to medical therapy. Endoscopic evaluation was deferred.

Pulmonary involvement in Behçet's syndrome occurs in about 5% of cases and tends to be associated with disease exacerbation at other sites.[16,17] Patients usually present with hemoptysis associated with fever, chest pain, and dyspnea. The most common radiographic abnormalities are segmental infiltrates or rounded opacities that have been shown to correlate with regions of pulmonary hemorrhage.[16,17] When done, pulmonary angiography may show arterial thromboses, emboli, and aneurysms. Pulmonary vasculitis, possibly due to circulating immune complexes, is thought to underlie these manifestations. Clinical evidence suggests that anticoagulant therapy is contraindicated. Pulmonary hemorrhage was a prominent feature of our patient's illness. He did not undergo definitive angiographic evaluation.

Systemic corticosteroids continue to be useful therapy for most manifestations of Behçet's syndrome.[1,3,5] As happened in our patient, corticosteroid therapy often leads to rapid control of skin, mucosal, and joint inflammation. The management of severe Behçet's syndrome remains more problematic. Supplemental therapy with other immunomodulatory agents is often necessary to control

serious manifestations such as uveitis and meningoencephalitis and to reduce the incidence of long-term steroid toxicity.[5,7] Various oral agents including azathioprine, colchicine, cyclophosphamide, chlorambucil, levamisole hydrochloride, cyclosporine, thalidomide, and dapsone have been used for this purpose.[7,18-24] One report suggests that plasma exchange may be beneficial in maintaining disease remission.[25]

Because of the benefit of high-dose cytotoxic therapy in other diseases associated with fulminant necrotizing systemic vasculitis, such as Wegener's granulomatosis and polyarteritis nodosa,[26] we chose to administer pulse-dose intravenous cyclophosphamide to our patient in an attempt to arrest the course of his illness. Although the possibility of a coincidental spontaneous remission cannot be excluded, this treatment, in conjunction with immune globulin and high-dose corticosteroid therapy, was followed by a dramatic clinical remission. After gastrointestinal motility had recovered, maintenance therapy with oral chlorambucil and prednisone was initiated. There has been no evidence of serious disease relapse during the 12 months of subsequent care, although recurrent arthritis and genital ulcers have justified ongoing therapy.

REFERENCES

1. Conn DL, Hunder EG, O'Duffy JD: Behçet's disease, *In* Kelley WN, Harris ED, Ruddy S, Sledge CB (Eds): Textbook of Rheumatology, 4th edition. Philadelphia, Pa, WB Saunders, 1993, pp 1097-1102

2. Shimizu T, Ehrlich GE, Inaba G, Hayashi K: Behçet disease (Behçet syndrome). Semin Arthritis Rheum 1979; 8:223-260

3. James DG: 'Silk route disease' (Behçet's disease). West J Med 1988; 148:433-437

4. Arbesfeld SJ, Kurban AK: Behçet's disease: New perspectives on an enigmatic syndrome. J Am Acad Dermatol 1988; 19:767-779

5. O'Duffy JD: Vasculitis in Behçet's disease. Rheum Dis Clin North Am 1990; 16:423-431

6. International Study Group for Behçet's Disease: Criteria for diagnosis of Behçet's disease. Lancet 1990; 1:1078-1080

7. O'Duffy JD, Robertson DM, Goldstein NP: Chlorambucil in the treatment of uveitis and meningoencephalitis of Behçet's disease. Am J Med 1984; 76:75-84

8. Danzi JT: Extraintestinal manifestations of idiopathic inflammatory bowel disease. Arch Intern Med 1988; 148:297-302

9. Tolia V, Abdullah A, Thirumoorthi MC, Chang CH: A case of Behçet's disease with intestinal involvement due to Crohn's disease. Am J Gastroenterol 1989; 84:322-325

10. Kasahara Y, Tanaka S, Nishino M, Umemura H, Shiraha S, Kuyama T: Intestinal involvement in Behçet's disease: Review of 136 surgical cases in the Japanese literature. Dis Colon Rectum 1981; 24:103-106

11. Yazici H, Tüzün Y, Pazarli H, et al: Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behçet's syndrome. Ann Rheum Dis 1984; 43:783-789

12. Cho KH, Shin KS, Sohn SJ, Choi SJ, Lee YS: Behçet's disease with Sweet's syndrome-like presentation—A report of six cases. Clin Exp Dermatol 1989; 14:20-24

13. Sobel JD, Haim S, Shafrir A, Gellei B: Cutaneous hyperreactivity in Behçet's disease. Dermatologica 1973; 146:350-356

14. Yazici H, Chamberlain MA, Tüzün Y, Yurdakul S, Müftüoglu A: A comparative study of the pathergy reaction among Turkish and British patients with Behçet's disease. Ann Rheum Dis 1984; 43:74-75

15. Yurdakul S, Yazici Y, Tüzün Y, et al: The arthritis of Behçet's disease: A prospective study. Ann Rheum Dis 1983; 42:505-515

16. Efthimiou J, Johnston JC, Spiro SG, Turner-Warwick M: Pulmonary disease in Behçet's syndrome. Q J Med 1986; 227:259-280

17. Cadman EC, Lundberg WB, Mitchell MS: Pulmonary manifestations in Behçet syndrome. Arch Intern Med 1976; 136:944-947

18. Yazici H, Pazarli H, Barnes CG, et al: A controlled trial of azathioprine in Behçet's syndrome. N Engl J Med 1990; 322:281-285

19. Raynor A, Askari AD: Behçet's disease and treatment with colchicine. J Am Acad Dermatol 1980; 2:396-400

20. Buckeley CE, Gillis JR: Cyclophosphamide therapy of Behçet's disease. J Allergy Clin Immunol 1969; 43:273-283

21. de Merieux P, Spitler LE, Paulus HE: Treatment of Behçet's syndrome with levamisole. Arthritis Rheum 1981; 113:372-373

22. Masuda K, Nakajima A, Urayama A, Nakae K, Kogure M, Inaba G: Double-masked trial of cyclosporin versus colchicine and long-term open study of cyclosporin in Behçet's disease. Lancet 1989; 1:1093-1096

23. Jorizzo JL, Schmalstieg FC, Solomon AR: Thalidomide effects in Behçet's syndrome and pustular vasculitis. Arch Intern Med 1986; 146:878-881

24. Sharquie KE: Suppression of Behçet's disease with dapsone. Br J Dermatol 1984; 110:493-494

25. Rifle G, Tanter Y, Mousson C, et al: Treatment of severe Behçet's disease by plasma exchange with or without immunosuppressive drugs—Long term follow-up. Prog Clin Biol Res 1990; 337:331-335

26. Haynes BF, Allen NB, Fauci AS: Diagnostic and therapeutic approach to the patient with vasculitis. Med Clin North Am 1986; 70:355-368